UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,190	01/24/97	JOSEL H	P564-7002

HM21/1105

NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
SUITE 330 G STREET LOBBY
655 FIFTEENTH STREET NW
WASHINGTON DC 20005-5701

EXAMINER	
RICIGLIANO,J	
ART UNIT	**PAPER NUMBER**
1648	4

DATE MAILED: 11/05/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary

Application No.	Applicant(s)
08/776,190	Josel et al.
Examiner	**Group Art Unit**
Joseph W. Rigiano Ph. D.	1648

☒ Responsive to communication(s) filed on *Mar 5, 1998*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *39-70* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-70* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Amendments Entered

1. Applicants' amendment and response, paper number 8, filed 8/19/98 have been entered. Claims 1-38 have been canceled previously. Claim 63 has been canceled by the amendment of 8/19/98.

Claims 39-62, and 64-70 are pending in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of applicants amendment, the rejection of claims 27-30 under 112 second paragraph is rendered moot.

Claim Rejections - 35 USC § 102

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 60 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al* for reasons of record in paper number 9

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 61 originally presented as claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* in view of Buchardt *et al* for reasons of record in papers 7 and 9.

Response to Arguments

7. Claims 60 and 62 originally presented as 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al* for reasons of record in paper numbers 7 and 9.

Applicants assert that Smith *et al* do not teach the introduction of marker groups or haptens into a carrier, especially in the case where the groups are attached to a primary amino or thiol group. However, applicants' attention is directed to the figure spanning columns 37 and 38. Applicants will note that Smith *et al* teach the addition of either Eosin or Texas Red to the amino terminus of a nucleotide chain. As indicated in the office action of 12/09/97 (page 4 of paper 7) the dyes (in that case fluorescein) can be both a hapten and a marker group. Therefore, Smith *et al* anticipate the invention of claims 60 and 62 for the reasons above and for the reasons of record in papers 7 and 9.

8. Claims 61 originally presented as claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* in view of Buchardt *et al* for reasons of record in papers 7 and 9.

Applicants have asserted the rejection of claim 61 (original claim 22) is flawed based upon flaws in the Smith *et al* reference. Applicants' attention is respectfully directed *supra* to the response to arguments with respect to rejection of claims 60 and 62 over the Smith reference under 102(b).

9. Applicants' arguments filed 8/19/98 in paper number 10 have been fully considered but are not found persuasive

Therefore claims 60-62 are rejected for the reasons above and for the reasons of record in paper number 9.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 39-62, and 64-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39-62, and 64-70 are rejected for reciting a peptide nucleic acid. The recitation is unclear because the specification at page 7 recites a peptide nucleic acid has a backbone made of the same or different monomeric units of a given formula and also that peptide nucleic acids have and their production are described in WO92/20703. The WO reference clearly embodies far more embodiments than the formula recited. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Claims 55, 56 and 66 are rejected because it recites that a hapten is an immunologically reactive molecule. This appears to be contradictory to the accepted definition of a hapten which is

a molecule which in the absence of a carrier cannot produce an immune response and hence cannot be immunologically reactive. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "hapten" in claims 55, 56 and 66 is used by the claim to mean "an immunologically reactive molecule," while the accepted meaning is "a molecule which cannot stimulate a specific antibody response" an hence cannot be immune reactive. See the attached definition as recited in the Textbook of Immunology 6th ed.

Claim 56 is recites that a hapten can be selected from a group of molecules including metabolites and mediators. Metabolites and mediators are vague and indefinite because it is unclear what they metabolites are formed from and what limitations apply to "metabolites" or "mediators." Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Claim 60-60 and 64-65 recites one of the following steps a and b are conducted. This is vague and indefinite because it is unclear what steps are to be conducted. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Specification

12. The disclosure is objected to because of the following informalities: The disclosure is objected to for failing to have a section titled a "brief description of the drawings." Appropriate correction is required.

13. The abstract of the disclosure is objected to because it fails to convey a concise statement of the technical disclosure of the patent.

14. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

Correction is required. See MPEP § 608.01(b).

15. The specification is objected to for not having a Summary of the invention as required by 37 CFR 1.73. A brief summary of the invention indicating its nature and substance, which may include a statement of the object of the invention, should precede the detailed description. Such summary should, when set forth, be commensurate with the invention as claimed and any object recited should be that of the invention as claimed.

16. Applicant is requested to review the disclosure to ensure it meets the formal requirements in MPEP 608.

17. Applicant is reminded of the appropriate contents of the specification

(a) Title of the Invention: See 37 CFR 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.

(d) Reference to a "Microfiche Appendix": See 37CFR 1.96(c) and MPEP § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely

known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet. (37 CFR 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.

(l) Sequence Listing: See 37 CFR 1.821-1.825.

Claim Rejections - 35 USC § 103

18. Claim 39, 41-51, 54-62, and 64-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchardt *et al* WO 92/20703 in view of Bredehorst *et al* (Analytical Biochem 193:272-279).

Buchardt *et al* teach the synthesis and use of peptide nucleic acids or PNA (which reads on nucleotide analogs) wherein the PNA is at made of at least 2 monomers (page 5 line 2), and in a preferred embodiment the length is from 2-61 (page 7 line 10). Buchardt *et al* teach that PNA molecules may be conjugated to reporter ligands including: alkylators, fluorescent compounds, spin labels or protein recognition ligands such as biotin or haptens, which read on marker groups, haptens or solid phase binding groups coupled to reactive side chains (page 20 starting at line 26). Moreover, Buchardt *et al* teach that the L groups (see figure III page 3 for example), which read on groups coupled to reactive side chains, can be a fluorophore, radio or spin label or protein-

recognizing ligand such as biotin or a hapten (page 19 lines 5-8). In that each L group is specifically located on the molecule in a location which is determined by the synthetic process under the control of the researcher these groups must be at predetermined positions.

With respect to the dependent claims Buchardt *et al* teach that the oligomers of their invention can be from 2-61 monomers (see page 7, structure III and line 10) which reads on the limitations of claims 41 and 42. In that L groups are explicitly recited as being haptens or fluorophores and as many as 61 L groups are present in a recited preferred embodiment, Buchardt *et al* meet the limitations of claims 43- 44. Buchardt *et al* (which applicants recite as teaching PNA molecules at page 7 of their specification) specifically recite that the molecules of their invention are nucleic acid analogs (see page 1, first line of the specification), therefore, Buchardt *et al* read on the nucleotide analogs of claim 45, 46. Buchardt *et al* teach that the molecule of their invention may be used in a method of capturing a nucleic in a hybridization assay (page 9 line 14 to page 10 line 36), thus the conjugate must be present as a double strand reads on claims 47-48.

Buchardt teaches that the L groups are attached to "A" groups which read on the reactive side groups of the instant claims (see structures III-VI). "A" groups are defined on page 5 lines 11-36 as having amino and alkylthio substitutents and therefore read on the limitations of claims 49. In that L is specifically recited as being a fluorophore or biotin Buchardt *et al* read on claims 50 and 51. In that the L groups, which may be haptens as discussed above, are selected from groups including aromatic moieties, which includes simple molecules such as catechol, Buchardt *et al* renders obvious the inventions of claims 55 and 56 since catechol has a MW of 110 and is

both a pharmacologically active compound and a neurotransmitter. Buchardt *et al* teach that the molecules of their invention can be conjugated to a peptide, protein or oligonucleotide which reads on the inventions of claim 57-59

Buchardt teaches the synthesis of PNAs (page 23 line 8 through page 27). Buchardt *et al* teach that the oligomers may be conjugated to, or that the L groups may be: markers, solid phase binding group or haptens (e.g. as discussed above, fluorophores, spin labels, radioactive labels, protein recognition ligands, biotin or haptens; page 20 lines 26-30). Buchardt teaches in reference to the incorporation of a detectable label "all those methods for labeling peptides, DNA and/or RNA which are presently known may in general terms be applied to PNA's" (page 14 lines 7-9) and the use of protecting groups in PNA synthesis (page 23 line 8 through page 27) and the use of protecting groups specifically associated with the L group (page 19 lines 9-14). Buchardt *et al* specifically teach modification of the terminal groups, one of which must be an amine, (page 20 lines 17-25). Therefore Buchardt *et al* reads on the inventions of claims 60-62 and 64-65.

Buchardt *et al* teach the formation of PNA DNA hybrids and PNA hybridization which reads on the immuno assays of claims 66-68 (page 13 -14). Buchardt teaches the ability to immobilize a PNA and to displace a strand of the complex and the incorporation of antigen labels which reads on a competitive immunoassay which read on claims 69 and 70.

Buchardt *et al* do not specifically teach that the peptide nucleic acids are helical as required by claim 54. However, in that the conjugates are drawn to the nucleic acid analogs known as peptides nucleic acids disclosed by Buchardt *et al* and that PNA molecules can hybridize to form double stranded molecules with other nucleic acids. Thus, since nucleic acids

are known to hybridize into helical structures it appears that PNA molecules must be inherently capable of forming this structure. Therefore, the burden is upon applicant to show an unobvious difference as required in MPEP 2112.

Buchardt *et al*, while teaching that multiple groups may be incorporated into or conjugated to a PNA molecule, does not explicitly recite incorporating both marker groups and haptens or solid phase binding groups into a single polymeric conjugate molecule.

However, Bredehorst *et al* teach the formation of carrier molecules (conjugates) formed from amino acids with both hapten and multiple marker molecules placed at specific positions see figure 1.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to incorporate both hapten and marker molecules as taught by Bredehorst *et al* in a PNA which is nucleic acid analog as taught by Buchardt *et al* because Buchardt *et al* teach the incorporation of haptens and markers into PNA molecules at selected sites and Bredehorst *et al* teach that is it known in the art to incorporate both a hapten and a marker into the same conjugate. One of ordinary skill in the art would have been motivated to do so in order to provide for a sensitive immuno assay of haptens which can quench the fluorophore markers without loss of sensitivity as taught by Bredehorst *et al*. One of ordinary skill in the art would have reasonably expected to be successful because the successful synthesis of PNA molecules incorporating multiple functionalities at specific positions and the incorporation haptens or markers had previously been taught by Buchardt *et al* and the required placement of a hapten at

position distant enough to prevent quenching of the marker fluorphore would be readily achieved with a PNA molecule.

19. Claims 40, 50 and 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buchardt *et al* in view of Bredehorst and further in view of Bard *et al*.[US 5,310,687, filed 11/4/98].

See the teaching of Buchardt *et al* as applied to claims 39, 41-52, 54-62, and 64-70 under 35 U.S.C. 103(a) as being unpatentable over Buchardt *et al* in view of Bredehorst *et al* supra.

In addition to the teachings above Bredehorst *et al* specifically recite the incorporation of negatively charge groups (ie. , SO3-, see figure 1) and the use of amino acid based conjugates and Buchardt *et al* teach the attachment of positive charged (polylysine) and negative charged (carboxyl or sulfo groups) to the carrier molecule; page 20 lines 17-25.

Buchardt *et al* in view of Bredehorst *et al* do not teach the use of luminescent metal chelates as required in an alternative embodiment in claim 50 or as a specific limitation of claims 40, and 52-53.

However, Bard *et al* teach the use of luminescent metal chelates as a marker with superior properties for use in assays (See the summary of the invention starting in column 5).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made use the luminescent metal chelates of Bard *et al et al* in the conjugates as taught by Buchardt *et al* in view of Bredehorst *et al* because Buchardt *et al* in view of Bredehorst *et al* teach the incorporation of marker groups into conjugates for immuno assays and Bard *et al* teach the incorporation of luminescent metal chelates into molecules for detecting analyte in

immuno assays formats. One of ordinary skill in the art would have been motivated to incorporate the luminescent metal chelates of Bard *et al* in conjugates as taught by Buchardt *et al* in view of Bredehorst *et al* in order to take advantage of the rapid efficient and sensitive detection permitted by the chemiluminescent markers taught by Bard *et al* (see abstract). One of ordinary skill in the art would reasonably expected to be successful because Bard *et al* had previously incrporated and applied the chemiluminescence metal chelates to a variety of assays including immunoassay.

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph. D., can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

PONNATHAPURA ACHUTAMURTHY
PRIMARY EXAMINER
GROUP 1800